## REMARKS/ARGUMENTS

After entry of this amendment claims 33, 56-59, 61, 63-128 are pending, claims 68-128 having been added and claims 34, 56 and 57 having been canceled. The claims have been canceled as redundant in view of claim amendments.

Support for amendments to claim 33 is provided *e.g.*, as follows: DNA, p. 25, line 8; promoter and enhancer, p. 35, line 9; and, multiple occasions, p. 28, line 18. Certain other amendments in the sequence of recited elements have been made for consistency. The term "preventing" has been deleted from claim 33. Support for new claim 68 is found, *e.g.*, at page 3, line 3.

Support for new claim 69 is found, *e.g.*, at page 28, lines 14-19. Support for new claim 70 is found, *e.g.*, at page 28, lines 17-21. Support for new claim 71 is found at *e.g.*, p. 33, lines 22-27. Support for new claim 72 is provided at *e.g.*, p. 3, line 7. Support for new claim 73 is provided at *e.g.*, p. 25, line 31. Support for new claim 74 is provided at *e.g.*, p. 25, line 33. New independent claim 75 is the same as claim 33 except that it refers to a method of prophylaxis instead of a method treating. Support for prophylaxis is provided at *e.g.*, p. 26, line 20. New claims 76-92 depend from claim 75 in parallel with corresponding claims depending from claim 33. Support for new independent claims 93 and 11 is provided at, *e.g.*, p. 25, line 10. New independent claim 111 is the same as claim 93 except that it refers to a method of prophylaxis instead of a method treating. New claims 94-110 depend from claim 93 in parallel with corresponding claims depending from claim 111. The claim amendments should not be construed as acquiescence in any ground of rejection.

Applicants' citation of the references has included all the elements required to comply with 37 C.F.R. §§ 1.97-98 that are known to them.

Claims 33-34 and 56-67 stand rejected for alleged lack of enablement. The Examiner raises a number of separate points, which will be addressed in turn.

The Examiner first alleges that the claims lack enablement in not requiring both a heavy and light chain. This basis of rejection has been rendered moot by amendment of the claims to that heavy and light chains are expressed to form an antibody.

Next, the Examiner alleges the claims lack enablement as including use of RNA rather than DNA, and in not specifying regulatory elements, such as promoters and enhancers. With respect to the first point, the claims have been amended to specify that the DNA is RNA to speed prosecution. With respect to the second point, applicants agree that a skilled artisan would know that various regulatory elements are needed to obtain expression of a coding sequence. Applicants also not that "[c]laims need not recite...factors where one of ordinary skill...would consider them obvious." *In re Skrivan*, 166 USPQ 85 (CCPA 1970). Nevertheless, to speed prosecution, the claims have been amended to specify that the DNA is operably linked to an enhancer and promoter to speed prosecution.

Next, the Examiner alleges that 61 and 67 may not be properly dependent on claim 33 in view of the specification teaching that the 10D5 antibody binds to an epitope in Aβ1-16. However, subsequent work has determined that the epitope of 10D5 is within residues 3-76 (*see* WO 00/72880, cited as cite no. 322 in the IDS filed June 2, 2003). Therefore, claims 61 and 67 do further limit claim 33.

Next, the Examiner alleges the claims are broad and read on any known route of administration and site of administration. The Examiner also refers to the claims including numerous viral and nonviral expression systems. The Examiner alleges that direct administration of a protein is more predictable than that of a nucleic acid encoding the antibody. The Examiner alleges that numerous factors complicate therapeutic expression of genes including the fate of the DNA vector, the in vivo consequences of altered gene statement and protein function, the fraction of vector taken up, the trafficking of genetic material within organelles, the rate of degradation of DNA, the level of mRNA produced, the stability of mRNA and protein and that these factors depend on the method of administration, site of administration and the disease treated. The Examiner alleges additional problems relating to inefficiency of transfection, anti-vector host immune responses and transient gene expression (citing to Verma). The Examiner also alleges that selection of appropriate promoters and enhancers is critical but a matter of trial and error. Marshall is cited as teaching that many problems must be solved before gene therapy is generally useful. Orkin is cited as teaching that none of the available vector systems is entirely satisfactory and that clinical efficacy had not been demonstrated. The

Examiner concludes based on the alleged unpredictability in obtaining therapeutic levels of antibody using vectors available at the time of filing, the breadth of claims and lack of working examples that undue experimentation would be required.

The presently claimed methods represent a relatively undemanding form of gene therapy because all that is required is the accumulation of antibody in the blood for a relatively short period. Although the underlying pathology treated by the presently claimed methods exists in the brain, the specification shows that delivering antibody to the blood stream achieves the desired result of modifying pathology in the brain (*see* Example XI at p. 70 et seq.). The relative simplicity of merely accumulating a protein in the blood versus expressing a vector in a specific cell type versus is noted by the Verma reference cited by the Examiner (*see* p. 239, column 1, third paragraph). The reference points out that protein accumulates in the blood from expression via in a number of different cell types including muscle, liver cells, fibroblasts and blood cells themselves. Also, the accumulation of a protein in the blood allows for easy assessment of its levels, and consequent adjustment of dosage and/or frequency of administration to suitable levels. Thus, treating diseases by accumulation of a protein in the blood is viewed as being relatively simple: "to correct blood-clotting disorders, such as haemophilia, *all that is needed* is a therapeutic level of clotting protein in the plasma" (p. 239, first column, third paragraph, emphasis supplied). Indeed, for these reasons, it may be inaccurate to characterized applicant's claimed methods as gene therapy.

The presently claimed methods also represent a relatively undemanding form of gene therapy in that they do not require permanent expression of an introduced gene or integration of an introduced gene into a patient genome, as is the case in many forms of gene therapy. By contrast, the present methods require only a relatively short period of treatment (*e.g.*, a phase I exploratory trial) to result in a statistically significant effect, and this effect is observed notwithstanding considerable variability in levels of antibody in the blood between patients (*see* Koller declaration at paragraphs (2) and (6)).

In view of the nature of the present methods, it is submitted that an unduly high standard of enablement is being applied. Most of the Examiner's comments are addressed to the enablement of the field of gene therapy as a whole, and not the particular application reflected by

the present claims. Further, the standard for patentability is considerably lower than that for FDA approval and does not require that a system be "entirely satisfactory," free from side effects or to have demonstrated clinical efficacy. *In re Brana,* 34 USPQ2d 1436 (Fed. Cir. 1995). Such is recognized by the Patent Office having granted over 1034 patents on gene therapy by July 2001, many of which have priority dates before that of the present application (*see Gene Therapy: Overcoming Enablement Rejections*, published by USPTO). These include a patent covering any viral gene therapy vector carrying the CFTR gene (*see* cited Orkin reference at p. 35, penultimate paragraph), notwithstanding that treatment of cystic fibrosis is considered by Verma and Marshall to be one of the more challenging forms of gene therapy (*see* Verma p. 239, column 1, third paragraph, Marshall, at p. 1052). Moreover, enablement does not require that generic claims function in every conceivable circumstance. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.* 224 USPQ 409 (Fed. Cir. 1984). The scope of enablement need bear only a reasonable correlation to the scope of the claims. *In re Fisher,* 166 USPQ 18, 24, (CCPA 1970).

The Examiner's comments present an unbalanced picture of the field of gene therapy, focusing on potential problems but ignoring the context in which the problems occurred or that the solutions already existed at the priority date of the application. For example, the Examiner alleges undue difficulty in selecting promoter-enhancer combinations, but omits to mention that this difficulty was in the context of trying to obtain expression in a specific tissue, mouse muscle, and was overcome by using a constitutive promoter from CMV (*see* Verma at p. 240, second column, second paragraph). Such a promoter is disclosed in the present specification (p. 25, line 12) and was also used in the previously cited Arafat reference to obtain production of antibody in the blood. The Examiner also refers to difficulties in immune responses and rejection, but omits to mention that such problems had been substantially reduced in adenovirus with later vector designs available by the priority date of the invention (*see* Verma at p. 241, paragraph bridging first and second column), and are not applicable to the other viral vectors commonly used in gene therapy, such as retroviruses (*see* Eck at p. 83, second column, first paragraph) and adeno-associated viruses (id. at p. 88, first column, third paragraph). Thus, for example, even by 1995, retroviral and adenoviral vectors had been used in hundreds of human patients (Eck at p. 83, column 1, second paragraph), and therapeutic amounts of factor

IX has been produced in the blood of mice for six months using AAV as a vector (*see* Verma at p. 241, third column first paragraph). Difficulties in immune response would also not be expected to be a problem for naked gene therapy, which is described as "feasible and highly promising" (Orr at p. 8, paragraph 6). Thus, Verma makes clear that as of 1997 gene therapy was not a field confronted with insurmountable problems but rather was close to entering mainstream medicine: "In the not too distant future, gene therapy will become as routine a practice as heart transplants today," p. 242, third column, last paragraph). Likewise, Orr quotes Dr. Shenk (not the inventor of the present application) as stating that a "moratorium on clinical trials is clearly not warranted." Orr at p. 34, paragraph 7. Consistent with the stated promise of gene therapy, it has been reported that over 800 approved gene therapy trials are being conducted worldwide (Nature 427, 779 (2004)).

Given a more balanced assessment of the state of gene therapy at the priority date of the application, the relatively undemanding nature of the presently claimed methods compared with gene therapy in general, and the less demanding standards for patentability versus FDA approval, it is submitted that the present claims are reasonably enabled across their scope. As discussed above, the presently claimed methods can treat amyloid pathology in the brain by delivery of antibody to the blood. As Verma makes clear, delivery to the blood can be achieved directly or indirectly. Direct delivery can be achieved by expressing a protein in the blood. Indirect delivery can be achieved by expressing the protein in other tissues, including muscle, liver cells, and fibroblasts, from which expressed protein is delivered into the blood. Thus, it is appropriate that the claims not be limited to any particular site of the delivery.

Given the number of different tissues to which DNA can be delivered, it is also appropriate that the claims be open to the several common delivery approaches, all of which can be used to deliver DNA to one or more sites suitable for ultimate delivery to the blood. In particular, the feasibility of using adenoviral vectors to deliver expressed antibody to blood is shown by the previously cited Arafat reference. The feasibility of using adeno-associated virus is shown by the experiments discussed in Verma relating to expression of factor IX in blood. Retroviruses are also known to be suitable for delivery to hematopoietic and other dividing cells (Eck at p. 85, column 1, second paragraph). The feasibility of using naked DNA to express

antibodies and other proteins is disclosed by US 5,558,859. The protein can be delivered by a variety of routes (*see* col. 7, lines 1-10), and released into the circulation (*see* col. 7, lines 50-55). The protein can be an antibody (*see* col. 10, lines 27-42). Similar disclosure is provided by US 5,817,637 describing immunization with DNA to express segments of HIV proteins.

Further, the difficulties in selecting promoter-enhancer combinations to give expression in a particular tissue discussed by Verma are not applicable to the present claims. Given that the presently claimed methods do not require tissue-specific expression, it is likely that any constitutive promoter including the exemplary CMV disclosed in the specification can be used. The feasibility of expressing an antibody in the blood using a CMV promoter is also shown by the previously cited Arafat reference. The Arafat reference also shows that concerns regarding appropriate intracellular trafficking and secretion are in fact not realized at least for single-chain antibodies to which the present claims are directed.

The Examiner criticizes the submission of Arafat as inadequate to show enablement in that Arafat was published four years after the priority date of the present application, the adenoviral vector he used was deficient in the E1 gene, the antibody was a single-chain antibody, and the antibody recognizes an antigen present on tumor cells and not in the brain. The Examiner notes that the sufficiency of disclosure is determined as of the filing date of an application. These points will be addressed in turn. First, that enablement is determined from the specification as filed does not preclude the applicant from providing evidence after the filing date which demonstrates that the claimed invention works (*see* MPEP § 2164.05). Here, Arafat was cited to show that recombinantly expressed antibody can properly fold. As noted above, it also shows the feasibility of using the CMV promoter disclosed by the present specification for accumulating antibody in the blood. Second, it was common practice to delete E1 and other genes from adenoviral vectors at the priority date of the invention (*see e.g.*, Eck at p. 86, second column, second paragraph, Verma at p. 241, first column second paragraph). A specification need not disclose and preferably omits what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1984). Third, although the ultimate pathologies being treated are different in Arafat and the present application (a tumor vs. amyloid deposits in the brain), the route of delivery can be the same. Both

approaches can be effected by delivery of antibody to the blood, and Arafat shows the feasibility of achieving this. Finally, although Arafat chose to express single-chain antibodies, there is no reason to expect that double-chain antibodies would not properly fold in a variety of cell types present in a patient. Antibodies have been successfully produced in a diverse cell types including mammalian cell cultures, transgenic animals, bacteria, plant cell cultures, transgenic plants and insect cells (*see* Schillberg, *Cell. Mol. Life Sci.* 60, 443-45 (2003) and Guttieri, *J. Immunol. Methods*, 246, 97-108 (2000), copies of which are attached hereto). Many of these cell types do not naturally express antibodies. Schillberg notes that full size antibodies and a variety of derivatives can be produced, and that all of these forms were successfully expressed even in plant cells (see pp. 434 and 436). Given that double chain antibodies can successfully fold even in insect cells and plant cells, there is no reason to expect otherwise in a variety of cell types in a patient, and particularly in the blood cells of a patient that naturally express antibodies.

Finally, the Examiner discounts the Koller declaration on the basis that it relates to administration of A$\beta$ peptide and not antibody nor nucleic acids encoding antibodies. In response, although it is agreed that the declaration relates to administration of A$\beta$ peptide, it is relevant to the present claims in two respects, as was noted above. First, it demonstrates that only relatively brief treatment was effective to achieve a statistically significant benefit (*see* paragraph (2) stating the results were obtained from an exploratory phase I trial). Second, this benefit was achieved not withstanding considerable variation in antibody response between different individuals (declaration at paragraph (6)).

For these reasons, it is submitted that the enablement is reasonably commensurate with the claim scope and the rejection should be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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